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Contributor Disclosures

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INTRODUCTION — Complex regional pain syndrome (CRPS) is defined as a disorder of the extremities characterized by regional pain that is disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is not restricted to a specific nerve territory or dermatome and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

The prevention and management of CRPS will be reviewed here. Other aspects of CRPS in adults and children are presented separately. (See "Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis" and "Complex regional pain syndrome in children" and "Overview of the treatment of chronic non-cancer pain".)

PREVENTION — There has been interest in preventive strategies for CRPS in high-risk groups, such as older patients with distal radius fractures. Vitamin C in particular has been suggested as a low-risk intervention that might accelerate fracture healing and limit excessive soft tissue injury via antioxidant mechanisms. Data in patients have been inconsistent, however.

Support for vitamin C is based on results of two randomized trials from the same group [1,2]. In the larger of the two trials, 416 older women with distal wrist fractures were randomly assigned to one of three daily doses of vitamin C (200, 500, or 1500 mg) or placebo for 50 days [2]. Over a one-year follow-up period, CRPS was less prevalent in those who received vitamin C (any dose versus placebo, 2.4 versus 10.1 percent). A subsequent trial of vitamin C (500 mg daily) versus placebo in 336 adults with acute distal radius fractures found no difference between groups in the rate of CRPS (8 percent in both groups), disability scores, and other functional outcomes at six weeks and one year post-fracture [3]. A meta-analysis of the three trials (n = 890) found a nonsignificant trend towards benefit of vitamin C (risk ratio 0.45, 95% CI 0.18-1.13) [4]. Overall quality of the evidence was assessed as low based on the low number of events and inconsistency among trials.

While vitamin C is a low-risk intervention, we do not find the evidence to be compelling enough to warrant routine use in all patients with distal fractures or other high-risk injuries. We counsel all adults with fractures to maintain adequate whole-food intake of protein, vitamin C, calcium, and vitamin D for six to eight weeks following fracture to promote healing. Vitamin C is reasonable to supplement for six to eight weeks after distal radius fractures in patients with poor baseline nutritional status or those who cannot comply with whole-food intake. A typical dose is 500 mg daily. (See "General principles of definitive fracture management", section on 'Overview and basic measures'.)

A 2009 clinical guideline from the American Academy of Orthopaedic Surgeons includes a moderate-strength recommendation for vitamin C in patients with distal radius fractures for the prevention of disproportionate pain but has not been revised since publication of the third randomized trial [5]. At least one CRPS guideline also includes a recommendation for vitamin C for preventive purposes [6].

Early mobilization after limb injury may also reduce the risk of CRPS, though there are no high-quality data to confirm benefit. Patients with fractures require accurate assessment of fracture healing to strike an appropriate balance between proper fracture healing, which requires a sufficient period of immobilization, and avoidance of prolonged immobilization, which increases the risk of complications. (See "General principles of acute fracture management" and "General principles of definitive fracture management", section on 'Fracture healing'.)

MANAGEMENT — A multidisciplinary approach is suggested for the management of CRPS [7,8]. Clinical experience suggests that treatment is more effective when begun in early in the course of the disease, ideally as soon as the diagnosis is established and before radiographic changes appear. However, it is uncertain whether immediate referral to a specialist in pain management results in superior outcomes compared with early physical or occupational therapy (OT) for protective and assisted mobilization of the affected limb within pain limits, supplemented by conservative pharmacologic interventions, and followed by referral to a pain management specialist if the patient does not improve. On the other hand, early referral to an interventional pain specialist for appropriate nerve block may reduce pain and enable patients with CRPS to tolerate aggressive physical therapy (PT).

Some interventions that are appropriate for all patients with CRPS include the following:

- Patient education (see 'Patient education' below)
- PT and OT, which are initiated as quickly as is practical following diagnosis of CRPS (see 'Physical and occupational therapy' below)

Patients with CRPS who have pre-existing or suspected psychologic or psychiatric issues and those who have insufficient improvement with physical, pharmacologic, and interventional therapies may benefit from psychosocial and behavioral management. (See 'Psychosocial and behavioral management' below.)

Pharmacologic and interventional procedures for pain control are utilized in an escalating fashion, beginning with those that are relatively safe and for which there is some evidence of effectiveness, and progressing to more risky interventions if a desired response is not achieved after a few weeks of therapeutic trial. The goals of pain management are to allow active participation in a rehabilitation regimen and to restore movement and strength of the affected limb.

For patients with early CRPS, we suggest starting with one or more of the following agents:

- A nonsteroidal anti-inflammatory drug (NSAID). A typical initial regimen is ibuprofen 400 to 800 mg three times a day or naproxen 250 to 500 mg twice daily. Dose adjustments must be made for older adult patients. (See 'Nonsteroidal anti-inflammatory drugs' below.)
- An anticonvulsant, such as gabapentin or pregabalin. (See 'Anticonvulsants' below.)
- A tricyclic or other antidepressant drug that is effective for neuropathic pain. We typically start with amitriptyline or nortriptyline (10 to 25 mg at bedtime or earlier in the evening if morning drowsiness occurs) and increase the dose, as tolerated. Other tricyclic antidepressants and dual uptake inhibitors that are indicated for treatment of neuropathic pain are alternatives to amitriptyline. (See 'Antidepressants' below.)
- Bisphosphonate treatment; intravenous (eg, clodronate 300 mg or pamidronate 1 mg/kg) or oral (eg, alendronate 70 mg weekly) bisphosphonates may be used. (See 'Bisphosphonates' below.)

- Topical lidocaine cream (2 to 5 percent) or topical capsaicin cream (0.025 to 0.075 percent), which may be discontinued if it is too irritating or if there is no benefit after three to five days of use. The author prefers topical lidocaine instead of capsaicin for most patients. (See 'Topical lidocaine and capsaicin' below.)

Referral to a pain management specialist with experience in management of CRPS is appropriate for patients with progressive symptoms and signs of CRPS who have an unsatisfactory response to the measures outlined above, as well as for patients with severe or chronic CRPS. Trigger point/tender point injections, regional sympathetic nerve block, spinal cord stimulation, or epidural clonidine may be the preferred intervention, depending upon the expertise of the specialist and the values and preferences of the patient. (See 'Interventional procedures' below.)

An alternative approach, suitable for patients with progressive CRPS who are unwilling to consider interventional procedures, is the sequential addition of different pharmacologic agents, including calcitonin and oral glucocorticoids, to the initial treatment regimen. (See 'Pharmacologic approaches' below.)

Patient education — Patient participation in physical and OT may be facilitated by an explanation that the pain associated with CRPS, which is presumably related to neuropathic and central mechanisms, does not indicate tissue damage in the hyperalgesic region but arises from an unknown cause. Prior to a referral to a specialist in rehabilitation or to a physical or occupational therapist, the clinician should stress the importance of working to regain use of the affected limb while recognizing the difficulty of doing so in the face of ongoing pain.

A support group available for patients and families in the United States is the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA).

Psychosocial and behavioral management — We suggest consulting a clinical psychologist if any of the following are present:

- CRPS of more than two months duration at presentation
- Insufficient response to treatment
- Suspected comorbid psychologic or psychiatric disorder

The goals of psychosocial and behavioral management include the following [9,10]:

- Identify any psychologic factors contributing to pain and disability
- Treat anxiety and depression
- Identify, explore, and proactively address any internal factors (eg, counter-productive behavior patterns) or external influences (eg, perverse incentives, family dynamics, etc) that may perpetuate disability or dependency
- Consider needs of family and caregivers and provide psychologic intervention and counseling where appropriate
- Provide a practical problem-solving, goal-orientated approach (involving both the patient and their family) to reduce barriers and promote healthy functioning

Although psychologic assessment and therapy have not been well studied in patients with CRPS, their usefulness in other chronic painful disorders suggests that this approach may be beneficial to those with CRPS. Patients with severe or chronic CRPS may benefit from cognitive behavioral therapy [9]. (See "Overview of the treatment of chronic non-cancer pain", section on 'Cognitive-behavioral therapy'.)

Case reports and personal experience suggest that a skilled hypnotherapist can be helpful for patients with heightened arousal, manifested by features of fear, anxiety, excessive sweating, and weakness, and in whom exercise is otherwise impossible [11,12]. Hypnosis allowed PT to progress in some patients with otherwise intractable disease.

Physical and occupational therapy — PT and OT are considered first-line treatments for CRPS [7,13,14], though most of the relevant studies are limited by methodologic problems, including but not limited to lack of control groups and small patient numbers [15,16]. A number of general therapeutic methods of PT and OT have been employed to treat CRPS, including but not limited to the following list [10]:

- General exercises and strengthening
- Functional activities
- Gait retraining
- Transcutaneous electrical nerve stimulation (TENS)
- Postural control
- Pacing, prioritizing, and planning activities
- Goal setting
- Relaxation techniques
- Coping skills
- Hydrotherapy
- Sleep hygiene
- Edema control strategies
- Vocational support
- Facilitating self-management of condition
- Splinting

There is no definitive evidence in favor of any of these methods [17]. Other rehabilitation techniques have been developed in centers with particular CRPS expertise [10]:

- Graded motor imagery [18-20]
- Pain-exposure PT [21] and graded exposure in vivo [22] to reduce pain avoidance behaviors
- Self-administered tactile and thermal desensitization with the aim of normalizing touch perception [23]
- Mirror visual feedback and immersive virtual reality [24-28]
- Functional movement techniques to improve motor control and awareness of affected limb position [29]
- Principles of stress loading [30]
- Conflict allodynia re-education to reduce fear of physical contact with others in community settings [31]

Perhaps the strongest evidence is for graded motor imagery, which led to significant reductions in pain and swelling in patients with CRPS in three small single-center randomized controlled trials [18-20]. However, a prospective observational study from two centers with a special interest in CRPS found no improvement in pain despite the use of graded motor imaging [32], suggesting it does not translate well into clinical practice [33].

Aside from cost and inconvenience, there is little downside to PT and OT for patients with CRPS. We suggest referral to an appropriate therapist immediately after the diagnosis is established. PT, which can be performed twice daily at home for patients in all stages of disease, should ideally begin before limitation of movement occurs in order to maintain range of motion and prevent contractures. Resting splints for the affected limb are sometimes used with a goal of preventing progressive joint contractures. However, the effectiveness of splinting is uncertain.

Pharmacologic approaches — Multiple treatment modalities are available to provide pain relief in patients with CRPS. The key to success is to use whatever works to reduce pain so that patients can tolerate PT. Pharmacologic agents that we use to treat CRPS include some agents in the following drug classes:

- NSAIDs (see 'Nonsteroidal anti-inflammatory drugs' below)
- Anticonvulsants (see 'Anticonvulsants' below)
- Antidepressants (see 'Antidepressants' below)
- Bisphosphonates (see 'Bisphosphonates' below)
- Topical lidocaine or capsaicin (see 'Topical lidocaine and capsaicin' below)
- Nasal calcitonin (see 'Calcitonin' below)
- Oral glucocorticoids (see 'Glucocorticoids' below)
- Other medication classes (see 'Others' below)

Nonsteroidal anti-inflammatory drugs — NSAIDs are often used in the initial treatment of CRPS, and some experts find them effective for some patients [7], but they are not well studied for this condition [6,34]. A typical initial regimen is ibuprofen 400 to 800 mg three times a day or naproxen 250 to 500 mg twice daily. Depending on the stage and severity of CRPS, NSAIDs are generally combined with any of the other agents listed below. For patients who cannot tolerate nonselective NSAIDs, the selective COX-2 inhibitors are alternative options.

Anticonvulsants — Anticonvulsants may be beneficial in neuropathic pain [6]. However, there are few data regarding efficacy in CRPS [17]. In one placebo-controlled randomized trial of 58 patients with CRPS, gabapentin (maximum 1800 mg daily) produced no significant improvement in pain [35]. Pregabalin can be used as an alternative to gabapentin. The key to using these medications is to start slowly and to titrate the dose as needed and tolerated; both drugs may cause dose-dependent dizziness and sedation that can be reduced by starting with lower doses and titrating cautiously. Pregabalin has been reported to cause euphoria, and is classified as a Schedule V controlled substance in the United States. (See "Overview of the treatment of chronic non-cancer pain", section on 'Anticonvulsants'.)

Although unproven in CRPS, the author's clinical experience suggests that gabapentin and pregabalin may be useful for pain management. However, other experts believe that gabapentin has only a marginal and clinically unimportant benefit for CRPS [36].

Antidepressants — Though not specifically studied in CRPS, antidepressant medications are often effective in reducing neuropathic pain [6]. The author's clinical experience suggests that tricyclic antidepressants reduce pain and are a valuable addition to PT for patients with CRPS. (See "Overview of the treatment of chronic non-cancer pain", section on 'Antidepressants'.)

Bisphosphonates — Bisphosphonates may be effective for reducing pain in patients with early CRPS who have abnormal uptake on bone scan, even though their positive effects in this condition are probably not related to their antiresorptive properties [17,37]. Supporting evidence comes from several small placebo-controlled randomized trials, including trials of intravenous and oral alendronate, intravenous neridronate, intravenous pamidronate, and intravenous clodronate [34,38-42]. Four of these trials enrolled only patients who had evidence of osteopenic or osteoporotic changes in the affected limb [38-40,42]. Illustrative trials include the following:

- The largest trial enrolled 82 subjects with CRPS of the hand or foot who had a disease duration of four months or less and abnormal uptake in early and late phases of three-phase bone scintigraphy [40]. The trial participants were randomly assigned to intravenous neridronate (100 mg given four times over 10 days) or placebo. At the end of the double-blind phase, 40 days after the first infusion, there was a significantly greater decrease in the visual analog pain scale for neridronate treatment group compared with the placebo group (-47 mm versus -22.6 mm). Neridronate also led to improvement on several secondary outcomes including indices of quality of life. The most common adverse events were acute-phase reactions (polyarthralgia and fever) with bisphosphonate administration; no serious adverse events were reported.

- Another trial randomly assigned 32 patients with early CRPS either to 300 mg of intravenous clodronate given daily for 10 days or to placebo [42]. After 40 days, pain decreased by a mean of 36 mm and 6 mm (on a 100 mm visual analog pain scale) in the clodronate and placebo groups, respectively, a difference that was statistically significant. The only side effect of active therapy was asymptomatic hypocalcemia in three patients.

Serious adverse effects of bisphosphonates include esophageal ulceration with oral use and osteonecrosis of the jaw. Patients who have difficulty swallowing, those with disordered esophageal motility, and those who cannot sit or stand for 30 minutes should not receive oral bisphosphonate therapy. Most reported cases of osteonecrosis have been in patients with malignant disease receiving potent intravenous bisphosphonates. However, osteonecrosis has been reported in some patients receiving oral bisphosphonates for benign disorders. (See "Risks of therapy with bone antiresorptive agents in patients with advanced malignancy", section on 'Osteonecrosis of the jaw' and "Osteonecrosis (avascular necrosis of bone)", section on 'Other risk factors'.)

Topical lidocaine and capsaicin — Topical application of lidocaine or capsaicin cream is used for treating neuropathic pain, but only limited data suggest efficacy in CRPS [6,43]. By analogy with treatment of painful diabetic neuropathy, lidocaine or capsaicin cream may be applied topically three to four times daily over painful areas. Local burning and skin irritation can occur with capsaicin, but this may become less of a problem with continued use.

Topical lidocaine and capsaicin are probably best suited for patients with early CRPS and mild to moderate pain despite the use of anticonvulsants, antidepressants, and/or NSAIDs. A treatment trial of three to five days may suffice to assess effectiveness and tolerability of these agents.

Calcitonin — The rationale for use of calcitonin involves the ability of this hormone to retard bone resorption and a putative analgesic effect. The mechanism responsible for analgesia is uncertain. (See "Calcitonin in the prevention and treatment of osteoporosis".)

There is conflicting evidence regarding the benefit of calcitonin for CRPS [17,34,37]. Calcitonin has been evaluated in three small placebo-controlled randomized trials for the treatment of CRPS, including two of nasal calcitonin [44,45] and one of subcutaneous calcitonin [46]. However, only one of these three trials detected benefit [45].

The optimal dose and duration of calcitonin treatment is uncertain. A dose of 300 international units daily was used in the one positive randomized trial [45]. If pain and/or function are improved with use, it can be continued, tapered, and discontinued as tolerated.

Considering the evidence for efficacy and the low risk associated with its use, we suggest calcitonin for patients with CRPS in combination with PT for patients who have mild or moderate symptoms despite the use of the agents listed above.

Glucocorticoids — Oral glucocorticoids (eg, divided doses of prednisone, 30 to 80 mg/day) may be effective for CRPS, but there is only low-quality evidence from small randomized trials with substantial methodologic limitations [17,34]. The findings of one small trial suggest that oral glucocorticoids are more effective than NSAIDs [47]. The trial randomly assigned 60 patients with CRPS following stroke to prednisolone (40 mg daily) or piroxicam (20 mg daily). At one month, a significantly greater proportion of patients in the prednisolone group than those receiving piroxicam met criteria for improvement (83 versus 17 percent, respectively).

Patients with chronic CRPS usually do not respond to glucocorticoids. Although the limited data discussed above suggest that glucocorticoids are more effective than NSAIDS for CRPS [47], we suggest using NSAIDs first and reserving use of glucocorticoids for those who do not respond to all the other aforementioned drugs.

Others — Other pharmacologic treatments for CRPS with limited evidence include alpha adrenergic drugs, ketamine, and intravenous immune globulin (IVIG).

- **Alpha-adrenergic antagonists and agonists** – Sympathetically maintained pain may respond to the addition of an alpha-1 adrenoceptor antagonist, which is supported by the clinical experience of the author and other experts [48]. The author has noted apparent benefit in some patients with the use of either prazosin (1 to 6 mg/day as tolerated) or phenoxybenzamine (10 to 30 mg/day as tolerated). Hypotension can be a limiting side effect of alpha-adrenergic blockers. The author has also treated patients using a clonidine patch (0.1 mg), which is changed every seven days, usually in combination with anticonvulsants and/or antidepressants; this approach has generally not resulted in significant side effects.

- Ketamine **infusion** – Systematic reviews have found that there is only low- to moderate-quality evidence supporting the use of ketamine for CRPS [17,34,49,50]. In one of the higher-quality randomized trials, ketamine infusion was compared with placebo in 60 patients with type I CRPS [51]. Patients assigned to five-day ketamine infusions had a statistically significant decline in pain scores from weeks 1 through 11 of follow-up compared with the placebo group, but the reduction was no longer statistically significant by week 12. Frequent side effects of ketamine in this trial included psychomimetic symptoms (eg, hallucinations, delirium), nausea, and vomiting.

- **Intravenous** immune globulin – IVIG does not appear to be beneficial for CRPS, despite promising preliminary studies. A single-center randomized trial involving 13 patients with CRPS found that low-dose IVIG reduced pain at 6 to 19 days following infusion by a modest degree compared with normal saline [52]. However, in a later multicenter randomized trial of 111 patients with chronic CRPS of one to five years duration, low-dose IVIG given for six weeks was not effective for pain reduction compared with placebo [53].

- **Opioids** – The use of opioids for neuropathic pain continues to be controversial, and there is a paucity of high-quality data supporting their efficacy for CRPS [6,54]. The use of opioids may be justified in select cases when other approaches have failed. Based on the author's clinical experience, there are patients who can benefit from a small dose of opioids in combination with other drugs for neuropathic pain described above. That said, escalating the dose can result in the risk outweighing the benefit.

Interventional procedures — Interventional procedures for the treatment of pain related to CRPS include trigger/tender point injections, regional sympathetic nerve block, spinal cord stimulation, epidural clonidine, and chemical or mechanical sympathectomy, among others. The published evidence for these methods, though generally limited and of low quality, does not support their efficacy. However, in the author's clinical experience, a number of patients derive meaningful benefit from these interventional procedures.

Patients receiving noninvasive therapy who are not improving are candidates for increasingly invasive interventions, allowing two weeks for improvement before moving on to the next type of treatment. In some tertiary centers, spinal cord stimulation, arguably the most invasive therapy, would be considered by 12 to 16 weeks from the time therapy for CRPS is initiated [55]. The author prefers to begin with sympathetic nerve blocks, and reserves the use of spinal cord stimulation for willing patients who do not respond to sympathetic nerve blocks.

Trigger point/tender point injections — Trigger/tender points may be found about the shoulder girdle when CRPS is limited to the upper limb. These trigger/tender points are located in the trapezius and suprascapular muscles in most patients. If unilateral involvement occurs, the other side can be used for comparison. The author's clinical experience is that trigger/tender point injections are sometimes effective and are safer than other treatment modalities. Injection of each trigger/tender point with local anesthetics with or without glucocorticoids is used for patients with early CRPS, before proceeding to more invasive and risky procedures.

Regional sympathetic nerve block — Temporary sympathetic nerve block may be accomplished by infiltration of a local anesthetic into the region of the sympathetic ganglia or by intravenous regional infusion of a sympathetic blocker, typically in combination with a local anesthetic. Sympathetic nerve block is an option at centers with expertise in this technique for patients with progressive symptoms and signs of CRPS who have an unsatisfactory response to the traditional measures outlined above. However, the limited evidence base for such treatment suggests there is no benefit. Despite what the literature shows, it is the author's experience, and that of many interventional pain physicians, that this procedure could be beneficial for many patients and indeed life changing for some.

- A systematic review updated in 2016 identified 12 studies with a total of 461 participants that evaluated the effect of sympathetic blockade with local anesthetics in children or adults with CRPS [56]. All the included studies were considered to have a high or unclear risk of bias. The following observations were noted:
  - Two small trials compared regional sympathetic nerve block with sham or placebo and found no significant difference for short-term pain reduction.
  - Two studies investigated regional sympathetic nerve block as an addition to rehabilitation treatment; only one of these reported pain outcomes and found no additional benefit from regional sympathetic nerve block.
  - Eight small randomized studies compared sympathetic blockade with a different active intervention. In most of these reports, there was no difference in between sympathetic block and other active treatments for pain outcomes.

- A 2010 guideline noted that intravenous sympathetic blockade with guanethidine for CRPS, as evaluated in eight small studies, had no added value for pain reduction compared with placebo [6].

Stellate ganglion blocks may be performed at one-week intervals and may be repeated several times. This treatment is abandoned if an immediate response (eg, improved temperature and decreased pain) does not occur following the first or second nerve block. Oral medications and intensive mobilizing PT should continue in patients who receive stellate ganglion blocks or intravenous regional (Bier) blocks. Each block should result in a longer duration of pain relief.

Spinal cord stimulation — Spinal cord stimulation (also termed "dorsal column stimulation") may be helpful if traditional therapeutic modalities fail [36], particularly in patients with disease limited to one extremity. In a randomized study of 36 patients and 18 controls, spinal cord stimulation plus PT reduced pain and improved health-related quality of life more than PT alone for up to two years but did not improve functional outcome measures [57,58]. No significant difference in pain was present during the period from three to five years following implantation [59]. Methodologic limitations of this trial include lack of sham intervention for control group and unblinded outcome assessment [60].

Complications of spinal cord stimulation are common and are mostly associated with improper positioning of the electrode. This technique should only be attempted at expert centers [36].

Epidural clonidine — Clonidine administered by epidural injection or infusion may reduce the pain of CRPS, but side effects such as hypotension and sedation can occur depending upon the dose [61,62]. Potential complications of epidural injection have limited study of this treatment to patients with severe refractory CRPS. In one trial, 26 patients with severe chronic CRPS that was unresponsive to sympathetic blocks were randomly assigned to epidural clonidine (300 or 700 microgram bolus injection) or to placebo and were assessed for up to six hours [62]. Epidural clonidine provided significantly greater pain relief than placebo injections. Pain relief was similar with both doses of epidural clonidine, though numeric pain scores were not provided in the report [17].

We suggest that epidural clonidine be used only for patients refractory to other, less invasive approaches. The author has experience in using clonidine in combination with local anesthetics for stellate ganglion and lumbar sympathetic nerve blocks successfully, but its value needs to be systematically studied.

Sympathectomy — Sympathectomy for CRPS has not been compared with placebo or sham surgery in randomized controlled trials [63]. Low-quality observational evidence suggests the possibility of benefit from chemical or surgical sympathectomy. However, sympathectomy is associated with high rates of adverse effects including increased pain, new neuropathic pain, and bothersome sweating [64].

In the author's experience, aggressive PT, pain management, and encouragement of the patient to work beyond the pain typically obviates the need for procedural treatments. Sympathectomy should be used only in patients who have shown a previous response to nerve blockade (eg, who have sympathetically dependent pain) and who are fully informed about the potential complications of the procedure.

Other modalities — Intrathecal baclofen may relieve dystonia in patients with CRPS [65], though data are limited [6]. Focal dystonia may also respond to botulinum toxin injections [7,14].

Hyperbaric oxygen therapy may be useful when skin breakdown and ulcer occurs in CRPS patients. However, it may take many sessions to achieve benefit, and only one randomized trial supports the use of this approach [66].

Recurrent CRPS — In patients with exacerbations or recurrence of CRPS due to exposure to cold, new surgery, or emotional trauma, small doses of tricyclic antidepressants (eg, amitriptyline or nortriptyline) and

anticonvulsants (eg, gabapentin or pregabalin) have been helpful in our experience. (See 'Pharmacologic approaches' above.)

Secondary prevention — There is limited evidence to guide strategies for the prevention and treatment of recurrences or relapses of CRPS. Elective surgery should be performed when features of previous episodes of CRPS have improved and when the patient is stable; surgery should be avoided during exacerbations. Additional perioperative and surgical strategies include maintenance of optimal perfusion of the affected limb, avoidance of tourniquet hemostasis, and perioperative intravenous infusion of mannitol. In one series of 47 patients with CRPS undergoing surgery involving a previously affected extremity, use of these measures was associated with a recurrence rate of CRPS of 13 percent. The recurrence was mild and temporary in five of the six patients in whom it occurred [67].

Other measures that have been proposed to prevent or minimize risk of recurrence include intensive rehabilitation, sympathetic block before surgery, regional anesthesia/analgesia techniques, pretreatment with perioperative calcitonin prophylaxis, and neuromodulation postsurgery [68-72]. However, the data supporting use of these approaches are limited. Most reports are of small case series, and some are limited to children. Thus, these approaches have not been tested in randomized trials, and it is uncertain whether the results in children can be generalized to CRPS in adults. CRPS in children is reviewed separately. (See "Complex regional pain syndrome in children".)

PROGNOSIS — The prognosis of CRPS is uncertain, with highly variable rates of poor and favorable outcomes in different studies. Nevertheless, a substantial proportion of patients have some degree of prolonged disability. The range of findings is illustrated by the following:

- In a population-based report of 102 Dutch patients with CRPS followed for an average of 5.8 years since disease onset, the following outcomes were observed [73]:
  - Ongoing CRPS fulfilling diagnostic criteria was present in 64 percent
  - Patients considered themselves as either recovered, stable, or worse due to progressive disease in 30, 54, and 16 percent of cases, respectively
  - Patients resumed their previous work completely, resumed work with adjustments, or were unable to work in 41, 28, and 31 percent of cases, respectively
- A retrospective population-based study of 74 cases of CRPS found that resolution of symptoms, sometimes spontaneously, occurred in 74 percent of patients [74]. Symptom duration ranged from 1 to 60 months (median 7 months).

Litigation and work-related compensation issues are involved in a substantial proportion of cases of CRPS cared for in tertiary pain management clinics, present in 17 and 54 percent, respectively, in one study in the United States [75].

Recurrence of CRPS is not uncommon; estimates of recurrence range from approximately 10 to 30 percent, with the higher rates occurring in younger patients, including children [76,77]. Recurrences can occur spontaneously or with cold exposure, but they also appear to be triggered by trauma or new surgery of the affected limb or of an unaffected remote site and by emotional trauma [68,69,77,78]. (See "Complex regional pain syndrome in children".)

In a study of 1183 consecutive patients with CRPS, recurrences were seen in 10 percent of patients [77]. The recurrence of CRPS occurred twice as often in a different limb than in the initial episode (76 patients) compared with recurrence in the originally affected limb that had become largely asymptomatic (34 patients). In 10

patients, CRPS started in symmetric limbs. Recurrences were usually spontaneous (53 percent) and were often associated with few signs and symptoms. Most of the remainder was associated with trauma or surgery (32 and 12 percent, respectively). The estimated incidence of a recurrence was 1.8 percent per patient per year.

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Neuropathic pain".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Complex regional pain syndrome (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Complex regional pain syndrome (CRPS) is defined as a disorder of the extremities characterized by regional pain that is disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is not restricted to a specific nerve territory or dermatome and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time. (See "Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis", section on 'Definition and terminology'.)

- Fractures are a common inciting injury for CRPS, and there is low-quality evidence that vitamin C may reduce the risk of CRPS in high-risk groups, such as older patients with distal radius fractures. We counsel all adults with fractures to maintain adequate whole-food intake of protein, vitamin C, calcium, and vitamin D for six to eight weeks following fracture to promote healing. In patients with distal radius fractures who have poor baseline nutritional status or who cannot comply with whole-food intake, we suggest vitamin C supplementation (Grade 2C). A typical dose of vitamin C is 500 mg orally daily for six to eight weeks after fracture. (See 'Prevention' above.)

- A multidisciplinary approach is suggested for the management of CRPS. Interventions appropriate for all patients with CRPS include patient education, physical therapy (PT), and occupational therapy (OT). (See 'Management' above and 'Patient education' above and 'Physical and occupational therapy' above.)

- Patients with CRPS who have pre-existing or suspected psychologic or psychiatric issues and those who have insufficient improvement with physical and pharmacologic therapies may benefit from psychosocial and behavioral management. (See 'Psychosocial and behavioral management' above.)

- Pharmacologic and invasive procedures for pain control are utilized in an escalating fashion, beginning with those that are relatively safe and for which there is some evidence of effectiveness, and progressing to more risky interventions if a desired response is not achieved after a few weeks of therapeutic trial. The goals of pain management are to allow active participation in a rehabilitation regimen and to restore

movement and strength of the affected limb. (See 'Management' above and 'Pharmacologic approaches' above.)

- For patients with early CRPS who require treatment for pain, we suggest starting with one (or more) of the following agents (Grade 2C):
  - Ibuprofen 400 to 800 mg three times a day or naproxen 250 to 500 mg twice daily (see 'Nonsteroidal anti-inflammatory drugs' above)
  - Amitriptyline or nortriptyline (10 to 25 mg at bedtime as initial dose for both) (see 'Antidepressants' above)
  - Gabapentin (starting dose of 100 mg at bed time for older adults and 300 mg at bed time for the rest, titrating the dose up as tolerated and needed) (see 'Anticonvulsants' above)
  - A bisphosphonate (eg, oral alendronate 70 mg weekly) for patients with early CRPS who have pain and abnormal uptake on bone scan (see 'Bisphosphonates' above)
  - Topical lidocaine cream (2 to 5 percent) or topical capsaicin cream 0.075 percent (see 'Topical lidocaine and capsaicin' above)
- Referral to a pain management specialist with experience in management of CRPS is appropriate for patients with progressive symptoms and signs of CRPS who have an unsatisfactory response to the measures outlined above. Depending upon the expertise of the specialist, trigger/tender point injections, regional sympathetic nerve block, spinal cord stimulation, or epidural clonidine may be the preferred intervention. (See 'Interventional procedures' above.)
- The prognosis of CRPS is uncertain, but a substantial proportion of patients have some degree of prolonged disability. (See 'Prognosis' above.)

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